IN THE SPECIFICATION

Please replace the paragraph beginning on page 2, line 19 with the following amended paragraph:

The most widely recognized monoclonal antibody targeting HER2 receptor function is marketed under the tradename Herceptin® (Genetech, Inc., San Francisco, Calif.). This recombinant humanized monoclonal antibody has high affinity for p185HER2. Early clinical trials with patients having extensive metastatic breast carcinomas demonstrate the ability of this monoclonal antibody to inhibit growth of breast cancer cells that overexpress HER2 (Baselga *et al.* (1996) *J. Clin. Oncol.* 14(3):737-744). In one such trial, monotherapy with Herceptin® in metastatic breast cancer patients yielded an overall response rate of 14% (2% complete responders and 12% partial responders). The median duration of response was 9.1 months, median survival was 12.8 months (ranging from 0.5 to 24+ months). Twenty-four percent of the patients were progression free at 5.8 months (Genentech, Inc., data on file). Degree of overexpression of p185HER2 was predictive of treatment effect. In another clinical trial, monotherapy with Herceptin® yielded objective responses in 5 out of 43 assessable metastatic breast cancer patients (11.6%) ~~(as cited in "Cancer and Leukemia Group B (CALGB) 9661, A Pilot Study of Low-dose Interleukin-2 plus Recombinant Human Anti-HER2 Monoclonal Antibody in Solid Tumors"; herein incorporated by reference)~~.

Please replace the paragraph beginning on page 5, line 15 with the following amended paragraph:

By "overexpression" of the HER2 receptor protein is intended an abnormal level of expression of the HER2 receptor protein in a cell from a tumor within a specific tissue or organ of the patient relative to the level of expression in a normal cell from that tissue or organ. Patients having a cancer characterized by overexpression of the HER2 receptor can be determined by standard assays known in the art. Preferably overexpression is measured in fixed cells of frozen or paraffin-embedded tissue sections using immunohistochemical (IHC)

detection. When coupled with histological staining, localization of the targeted protein can be determined and extent of its expression within a tumor can be measured both qualitatively and semi-quantitatively. Such IHC detection assays are known in the art and include the Clinical Trial Assay (CTA), the commercially available ~~LabCorp~~ LabCorp™ 4D5 test, and the commercially available DAKO HercepTest™ (DAKO, Carpinteria, Calif.). The latter assay uses a specific range of 0 to 3+ cell staining (0 being normal expression, 3+ indicating the strongest positive expression) to identify cancers having overexpression of the HER2 protein (see the Herceptin®. (Trastuzumab) full prescribing information; September 1998; Genentech, Inc., San Francisco, Calif.). Thus, patients having a cancer characterized by overexpression of the HER2 protein in the range of 1+, 2+, or 3+, preferably 2+ or 3+, more preferably 3+ would benefit from the methods of therapy of the present invention.

Please replace the paragraph beginning on page 27, line 7 with the following amended paragraph:

The functional consequences of IL-2 binding on NK cells is dependent upon the specific receptor complexes present. Activation of the high affinity heterotrimeric receptor with picomolar concentrations of IL-2 provides a proliferative stimulus, without augmenting cytotoxicity. In contrast, nanomolar concentrations of IL-2 that bind the intermediate-affinity beta-gamma IL-2 receptor complex result in augmented effector cell cytotoxicity, with little effect on proliferation. These functional results of IL-2 binding to its receptors are time dependent as well, with prolonged stimulation producing more pronounced effects ~~(see the references cited in "Cancer and Leukemia Group B (CALGB) 9661, A Pilot Study of Low-dose Interleukin-2 plus Recombinant Human Anti-HER2 Monoclonal Antibody in Solid Tumors," herein incorporated by reference and referred to as the CALGB 9661 Protocol)~~.

Please replace the paragraph beginning on page 27, line 18 with the following amended paragraph:

Meropol et al. ~~(reference 5 of the CALGB 9661 Protocol)~~ have demonstrated that PBMC may be expanded several fold *in vivo* with daily subcutaneous administration of IL-2, at doses that result in 10-100 pM peak levels with minimal toxicity. The maximum tolerated dose in this study was 1.25 MIU/m^2 daily. At daily doses ranging from 0.4-1.5 MIU/m^2, NK cell expansion from 154-530% above baseline was observed. In an effort to stimulate the cytotoxic mechanism in this expanded population, Meropol and Caligiuri (unpublished data) have administered 10-fold higher doses of IL-2 as outpatient pulses subcutaneously for three days every two weeks in patients receiving daily low-dose treatment. The maximum-tolerated "intermediate-dose" pulse in this schedule is 15 MIU/m^2. The intermediate-dose pulsing further augmented NK expansion *in vivo*. For patients treated with escalating intermediate pulse doses every two weeks, NK cell number rose from 226/μl to greater than 1,500/μl after pulsing. Dose-limiting toxicities with both low-dose IL-2 and intermediate-dose pulsing have been largely constitutional, with fever, chills, and fatigue predominating. Severe side effects observed with high-dose IL-2, such as capillary leak syndrome, renal failure, and hypotension requiring pressors did not occur. Thus, IL-2 doses capable of engaging intermediate affinity receptors (and hence stimulating effector cell cytotoxicity) may be safely administered to outpatients with expanded NK populations in repetitive fashion.

Please replace the paragraph beginning on page 28, line 5 with the following amended paragraph:

Natural killer cells expanded *in vivo* with low-dose IL-2 also commonly express Fc-gamma receptors and participate in antibody-dependent cellular cytotoxicity (ADCC). In principle, antibodies capable of binding both tumor targets (Fab) and PBMC (Fc) could help deliver effector cells to tumor sites, as well as augment cytotoxicity through ADCC. Recently, a humanized anti-HER2 monoclonal has become available for clinical use. This antibody recognizes an epitope overexpressed by at least 20% of a variety of tumor types, including breast, ovarian, gastric, non-small cell lung, and bladder. The antibody has high affinity for p185HER2, with Kd=0. 1 nmol/L. In an animal model, optimal inhibition of tumor cell growth was achieved with trough serum antibody concentrations of at least 10 μg/ml ~~(see reference 9 of~~

~~the CALGB 9661 Protocol~~). Humanized anti-p185HER2 participates in ADCC with PBMC's derived from patients treated with subcutaneous low-dose IL-2 ~~(see reference 10 of the CALGB 9661 Protocol)~~.

Please replace the paragraph beginning on page 28, line 18 with the following amended paragraph:

In a phase II study ~~(see reference 11 of the CALGB 9661 Protocol)~~, humanized anti-HER2 was administered to 46 patients with metastatic breast cancer at a weekly intravenous dose of 100 mg following a loading dose of 250 mg. Objective responses were seen in 5 of 43 assessable patients (11.6%), with stable disease reported in 16 additional patients. Antibody trough levels of at least 10 μg/ml were obtained in more than 90% of patients. The mean serum antibody half-life was 8.3 ± ~~??~~ 5.0 days. Human anti-human antibodies were not detected in this study. Toxicity was unusual in this study. Eleven moderate-severe toxic events occurred in 768 antibody administrations. These toxicities included fever and chills (5 patients), pain at tumor site (3 patients), diarrhea (2 patients), and nausea and vomiting (1 patient).

Please replace the paragraph beginning on page 29, line 2 with the following amended paragraph:

The IL-2 formulation used in this study is manufactured by Chiron Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin (SEQ ID NO:1), which differs from the native human IL-2 sequence in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by a serine residue (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from *E. coli*, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543. The IL-2 formulation marketed as Proleukin is supplied as a sterile, white to off-white preservative-free lyophilized powder in vials containing 1.3 mg of protein (22 MIU).

Please replace the paragraph beginning on page 30, line 17 with the following amended paragraph:

Patients enrolled in this study were required to have documented HER2 overexpression in tumor tissue at the time of enrollment. HER2 measurement was performed by immunohistochemical staining of pathology biopsy material previously obtained. HER2 overexpression was defined as a 2+ or 3+ staining with the ~~LabCorp~~ LabCorp™ 4D5 or DAKO HercepTest™ immunohistochemical stains.

Please replace the paragraph beginning on page 32, line 13 with the following amended paragraph:

Low-dose IL-2 was administered to expand the NK cell population *in vivo* and was given on an outpatient basis and patient self-administration was encouraged. Intermediate-dose IL-2 pulsing was administered in the outpatient setting by medical personnel, with careful monitoring as follows. Vital signs were obtained pre-IL-2 dosing and at 2-hour intervals after administration. Patients were observed for 8 hours on each day during the initial 3 day pulse sequence (days 8-10 of the introductory cycle). If no grade 3-4 toxicities were observed ~~(see definition of graded toxicities in the CALGB 9661 Protocol)~~ during course 1, in subsequent cycles the patient was monitored by observation for 8 hours on day 1, and 4 hours or days 2 and 3. If there was no toxicity greater than grade 2 observed on the first day, this monitoring was continued throughout treatment. If the patient experienced toxicity greater than grade 2, this 8-hour monitoring was continued on days 2 and 3. Additionally, vital signs were obtained immediately before antibody infusions, and every 30 minutes after an infusion begin, for 90 minutes.

Please replace the paragraph beginning on page 34, line 1 with the following amended paragraph:

Lymphocyte phenotyping was performed as follows. Red blood cells were lysed and fresh cells prepared for phenotypic analysis ~~as previously described (see citation 13 of CALGB~~

~~9661 Protocol~~). Monoclonal antibodies used included FITC-conjugated CD3 (Becton Dickinson, San Jose, Calif.), and PE-conjugated CD56 (Coulter Immunology, Hialeah, Fla.). Samples were subsequently collected on a FACScan and analyzed using the Winlist software program (Verity Software House, Inc.). Natural killer cells were identified as $CD3^{-}CD56^{+}$ using a lymphocyte gate ~~(see reference 14 of CALGB 9661 Protocol)~~.

Please replace the paragraph beginning on page 35, line 11 with the following amended paragraph:

Objective progression or relapse – An increase in the product of the perpendicular diameters of any measured lesion by greater than 25% over the size present at entry on study. For evaluable disease, any definite increase in tumor size. The appearance of any new areas of malignant disease. A 2-step deterioration in performance status, the appearance of CNS disease, greater than 10% loss of pretreatment weight, or increasing symptoms ~~as noted in the CALGB 9661 Protocol~~.

Please replace the paragraph beginning on page 36, line 19 with the following amended paragraph:

A total of 15 patients accrued to the 8.0 mg/kg biweekly antibody dose level. Six patients ended treatment due to progressive disease, without any major toxicities, after 25, 15, 4, 3, 3, and 2 cycles, respectively. One patient who ended treatment due to progressive disease after 14 cycles experienced severe nausea and vomiting during cycle 1 but was fine after a 25% intermediate IL-2 dose decrease. Four patients ended treatment due to toxicity: an intermediate dose DLT (rigors) after 2 cycles without dose reductions; an intermediate dose, DLT (shortness of breath) after 1 cycle (no dose reductions); a Grade 3 nausea, vomiting, and pain intermediate-dose DLT after 2 cycles with a dose reduction in cycle 2; and a low- and intermediate-dose DLT (elevated liver counts) after 2 cycles with dose reductions of both low and intermediate IL-2. One patient experienced a low-dose DLT and some pulmonary reaction to the initial HER2 dose. The low-dose IL-2 was reduced and pretreatment with ~~Benadryl~~ Benadryl™ was added. The

patient was fine for 8 additional cycles and then started to experience thrombocytopenia. The intermediate-dose was reduced and the patient received a total of 19 cycles with a complete response before voluntarily withdrawing. Three patients remain on treatment. One patient is on cycle 5 with a partial response and the other 2 are both on cycle 3.